REMARKS

Status of the Claims

Claims 1-12, 15-17, 23 and 27-45 are pending, with claims 1, 29 and 43 being independent. Claim 6 is canceled herein without prejudice or disclaimer thereto. Also, withdrawn claims 27, 28, 33-40 and 42 are canceled herein without prejudice or disclaimer thereto. Applicants reserve the right to file at least one continuation or divisional application directed to any subject matter canceled by way of the present Amendment.

Rejection under 35 U.S.C. § 112

Claim 6 stands rejected under 35 U.S.C. § 112, first paragraph. Claim 6 is canceled herein without prejudice or disclaimer. Thus, this rejection is moot.

Rejections under 35 U.S.C. § 103

Claims 1-12, 15-17, 23, 29-32, 41, and 43-45 stand rejected under 35 U.S.C. 103(a) as unpatentable over U.S. Patent 6,914,128 ("the '128 patent") in view of Gordon et al. (Gastroenterology, 2001, 121:268-274; "Gordon"). For reasons discussed below, the rejection based on these two documents is considered erroneous.

On page 4 of the Office Action dated November 20, 2007, the Office argues that the '128 patent discloses a stabilizing antibody formulation, suitable to enhance the shelf life or effectiveness of an antibody formulation for various

molecular targets. The Office then notes that Gordon discloses the natalizumab antibody, and argues that it would have been obvious to one of skill in the art to substitute the antibody of the formulation of the '128 patent with the natalizumab antibody as taught by Gordon. Applicants submit this is not the case.

In establishing a *prima facie* case of obviousness, there are two approaches currently used: (1) the analysis using the Graham factors and (2) the "teaching, suggestion or motivation" (TSM) test. Both tests are applied below.

Graham Factor Test

The four Graham factors outlined by the Supreme Court in *Graham v. John Deere Co.* 383 U.S. 1 (1966) are: (a) determining the scope and contents of the prior art; (b) ascertaining the differences between the prior art and the claims in issue; (c) determining the level of ordinary skill in the pertinent art; and (d) evaluating evidence of secondary considerations, including commercial success, long felt but unsolved needs, and failure of others.

(a) Determining the scope and contents of the prior art

One of ordinary skill in the art at the time of the invention would recognize that there was a need to provide a stable formulation for natalizumab. However, one of ordinary skill in the art at the time of the invention would not have been able to create such a formulation based on the art. The art teaches that antibodies are not readily interchangeable in formulations (*see* Cleland et

al., Critical Reviews in Therapeutic Drug Carrier Systems, 10(4):307-377 (1993), because each antibody has unique physical characteristics that differ in significant ways, including isoelectric point, solubility and conditions under which they aggregate. The art further fails to teach a stable formulation containing natalizumab or how to arrive at such a formulation. For example, Gordon, cited as the secondary reference in the present rejection, provides a formulation which is unstable, and accordingly is unusable.

(b) Ascertaining the differences between the prior art and the claims in issue

The Office argues one of skill in the art at the time the invention was filed would readily substitute natalizumab into the formulation of the '128 patent. Applicants submit this is not the case. Natalizumab is a humanized monoclonal IgG4 antibody which targets the α4 subunit of α4β1 and α4β7 cell surface receptors. In contrast, the antibody of the '128 patent is an IgG1 antibody that targets IL-12, a secreted cytokine. Natalizumab and the antibody of the '128 patent have different molecular targets, different constant regions and different variable regions.

Antibodies are not readily interchangeable in formulations (*see* Cleland et al., Critical Reviews in Therapeutic Drug Carrier Systems, 10(4):307-377 (1993), because each antibody has unique physical characteristics that differ in significant ways, including isoelectric point, solubility and conditions under which they aggregate. These unique differences require different formulations in

order to achieve maximum therapeutic efficacy as well as product stability. One skilled in the art cannot predict *a priori* whether a formulation would be effective for natalizumab, the antibody of the '128 patent, or any other antibody.

To this end, the Federal Circuit, in *Takeda v. Alphapharm*, No. 2006-1329 (Fed. Cir. 2007), stated that:

> A known compound may suggest its homolog, analog, or isomer because such compounds "often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties." We clarified, however, that in order to find a prima facie case of unpatentability in such instances, a showing that the "prior art would have suggested making the specific molecular modifications necessary to achieve the claimed invention" was also required. Id. (citing *In re Jones*, 958 F.2d 347 (Fed. Cir. 1992); *Dillon*, 919 F.2d 688; *Grabiak*, 769 F.2d 729; *In re Lalu*, 747 F.2d 703 (Fed. Cir. 1984)) [emphasis added].

In the present application, as noted, natalizumab and the antibody of the '128 patent are not structurally similar, but instead very different, having different constant regions, different variable regions, and different molecular targets. The '128 patent does not provide or suggest a reason for making any modifications necessary to arrive at the presently claimed invention.

Further, the '128 patent lists many formulation ingredients (*see* col. 72-76), but it does not teach why certain ingredients may be especially beneficial with particular antibodies or particular physical and chemical characteristics. The laundry list of ingredients in the '128 patent is so extensive that it becomes meaningless for developing a stable formulation of a specific antibody. There are an unlimited number of formulations that could be developed by selecting

various ingredients at various concentrations. However, the problem with the '128 patent in this instance is that there is no teaching as to which specific combination of ingredients would make a stable formulation of natalizumab.

Gordon is cited as disclosing natalizumab in formulations. However, the formulation disclosed in Gordon was found to be unstable and is no longer used. In other words, the Gordon formulation did not work. It follows, therefore, that it would not have been obvious to one of skill in that art at the time the invention was made to substitute the antibody of formulation of the '128 patent with the natalizumab antibody as taught by Gordon.

By way of support, Applicants refer to paragraphs 8-10 of the Declaration of David Burke, pursuant to 37 C.F.R. §1.132, filed on November 20, 2007 ("the Declaration"). Dr. Burke has worked with natalizumab and antibody formulations for many years.

(c) Determining the level of ordinary skill in the pertinent art

The level of ordinary skill in the pertinent art would be the one who works with formulations, and is skilled in the development and use of antibody formulations suitable for therapeutic administration.

(d) Evaluating evidence of secondary considerations, including commercial success, long felt but unsolved needs, and failure of others

The claimed formulation solves the stability failures present in Gordon, fulfills a long-felt but unmet medical need, and has attained commercial success. As discussed above, the formulation of the Gordon reference failed because it was not stable. Furthermore, as noted in paragraph 14 of the Declaration, the presently claimed marketed under the brand name Tysabri® is FDA approved for the treatment of relapsing forms of multiple sclerosis ("MS"). In MS, this drug is recommended for patients who have had inadequate response to previous therapies. Further, Tysabri® was FDA approved in January 2008 for treatment of moderately to severely active Crohn's disease. As of the first fiscal quarter of 2008, over 15000 patients were receiving Tysabri®, having about $160 million in U.S. sales.

TSM Test

To establish a *prima facie* case of obviousness under the "teaching, suggestion or motivation" (TSM) test, three basic criteria must be met. (MPEP § 2143) First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art references, when combined, must teach or suggest all the claim limitations.

There is no suggestion in either the cited references or the knowledge generally available to one of ordinary skill in the art, to substitute natalizumab for the antibody of the '128 patent. Neither the '128 patent nor Gordon provide a

stable formulation containing natalizumab appropriate for therapeutic administration.

Nor is there a reasonable expectation of success. As noted, antibodies are not readily interchangeable. The structural differences between the antibody of the '128 patent and natalizumab include differences in the constant and variable regions, as well as in the molecular target. Such differences require different formulations and concentrations in order to arrive at a stable, suitable formulation for medical use. Gordon does not remedy this deficiency, as Gordon discloses an unstable formulation of natalizumab that cannot be used. Further, the '128 patent does not teach how to modify the Gordon formulation to make it stable. Therefore there is no reasonable expectation of success in producing the applicants' invention based on the teachings in the cited prior art.

One of skill in the art would have to do more than routine experimentation to arrive at the claimed natalizumab formulation. As noted in paragraph 13 of the Declaration, natalizumab was very difficult to formulate into a stable product safe for administration to patients. The specific combination and concentration of ingredients was found only after years of experimentation and human clinical trials. In fact, it took Applicants approximately ten years to arrive at the claimed formulation.

Finally, to establish a *prima facie* case of obviousness, the prior art references must teach or suggest all the claim limitations. Neither the '128 patent nor Gordon teach or suggest combining the claimed stable formulations

containing natalizumab. Therefore, the cited references, either alone or combined do not teach or suggest all the claim limitations.

It follows, therefore, that it would not have been obvious to one of skill in the art at the time the invention was filed to substitute the antibody of the formulation of the '128 patent with the natalizumab antibody as taught by Gordon.

It is respectfully submitted that claims 1, 29, and 43 are patentable over the documents relied on by the Examiner for reasons discussed above. Dependent claims 2-12, 15-17, 23, 29-32, 41, and 44-45 are considered patentable as well.

If there are any questions regarding this amendment or the application in general, a telephone call to the undersigned would be appreciated since this should expedite the prosecution of the application for all concerned.

If necessary to effect a timely response, this paper should be considered as a petition for an Extension of Time sufficient to effect a timely response, and

please charge any deficiency in fees or credit any overpayments to Deposit Account No. 05-1323 (Docket #103930.B000119).

Respectfully submitted,

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Deborah H. Yellin
Registration No. 45,904

CROWELL & MORING LLP
Intellectual Property Group
P.O. Box 14300
Washington, DC 20044-4300
Telephone No.: (202) 624-2500
Facsimile No.: (202) 628-8844
DHY:gtm